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The Procter & Gamble Company
Ivorydale Technical Center
5299 Spring Grove Avenue, Cincinnati, Ohio 45217-

98 JUN 22 PM 3:02

June 17, 1998

Document Processing Center (TS-790)
Attention: Section 8(e) Coordinator
Office of Toxic Substances
U.S. Environmental Protection Agency
401 M Street, S. W.
Washington, D. C. 20460

Contains

This submission of information is made as required by TSCA Section 8(e) regulations and guidance.

The enclosed information does not, however, scientifically support the conclusion that the test material poses a substantial risk of injury to people or the environment.

This describes preliminary findings for Amines, C10-16-alkyldimethyl, N-oxides, CASRN 70592-80-2 from a dose-setting study conducted to identify appropriate dose levels for a definitive, larger scale developmental toxicity study. The correspondence from the laboratory includes unaudited summary information being communicated to us solely for the purposes of setting dose levels for the definitive study (see attached draft summary document). Of note, although maternal toxicity was observed in this dose-range finding pre-study, none of the information outlined alters the safety profile of the test substance.

As communicated to us by the contract laboratory conducting the study, in Group V (650mg/kg BW/d) four of eight rats were found dead (Gestation Days 7, 7, 8, 9) and a fifth rat was moribund sacrificed on GD 11. In Group IV (325 mg/kg/day), one of eight rats was found dead (GD 20). These deaths were considered to be related to the test substance because dosage-dependent clinical observations and body weight loss were noted before death. The toxicity observed at these two dosage levels was consistent with measured values for the acute toxicity of the test substance.

Group Mean Maternal Body Weight changes indicated all groups gained weight during the course of the study (Gestation Days 0-20), however the Group IV (325 mg/kg BW/d) and Group V (650mg/kg BW/d) weight gains were approximately 75 and 140 grams less than the comparable gain observed in the control group. There was no net weight gain experienced in Group V during the course of treatment (GD 6-12) and surviving rats in Group V continued to have reduced body weight gains during the postdosage period for this group (GD 14-20).

Body weights and body weight changes for the 32.5 and 100 mg/kg/day groups (Groups II and III) were comparable to control values throughout the gestation period.

Clinical observations considered test substance related in Group V (650mg/kg BW/d) included excess salivation, urine-stained abdominal fur, ptosis, and soft/liquid feces, as well as agonal signs of loss of righting reflex, and gasping in animals found dead or moribund sacrificed. Clinical observations considered test substance related in the one rat found dead (GD 20) in Group IV included excess salivation, chromorhinorrhea, labored breathing, urine-stained abdominal fur, and gasping. Clinical observations during gestation considered test substance related were: excess salivation at the 100, 325 and 650 mg/kg/day dosage level (Groups III, IV and V, respectively); perinasal substance, chromorhinorrhea, gasping, labored breathing and perioral substance in

Groups IV and V; ptosis, and soft or liquid feces in Group V. All clinical observations in Group II were considered unrelated to the test substance.

All conceptuses were resorbed in the two litters in Group V. Due to maternal morbidity/mortality, treatment was discontinued and these dams were only administered the test substance on GD 6-11 or GD 6-13.

Increased early resorptions with a concomitant reduction in litter size occurred in Group IV, relative to the control group. Group IV Mean Fetal Body Weight was reduced by approximately 10% when compared to the controls. No dead fetuses and no fetal gross external alterations were observed among the remaining litters in Group IV.

Other observations were not dosage-dependent and were not considered to be related to the test substance. This would include one litter in Group II (32.5 mg/kg/day) consisting of only three live male fetuses; inclusion of this litter tended to skew the values for implantations, litter sizes and fetal body weight in this group.

No Caeserian-sectioning or litter parameters were affected by dosages of the test substance as high as 100 mg/kg BW/day. There were no dead fetuses and no fetal gross external alterations observed at any of the dosages (Group I - V).

In summary, all observations observed are within the spectrum of effects expected for the test substance, under the exaggerated exposure conditions of this range finding study. No evidence of teratogenicity is apparent and nothing communicated to us thus far by the contract laboratory alters the safety profile of the test substance.

We have handled and will continue to handle this material with appropriate caution in our work environment in keeping with our standard procedures for handling all chemical substances. We will communicate appropriate hazard information for the test substance by both labels and MSDS.

If you wish further information, please contact me.

Very truly yours,

THE PROCTER AND GAMBLE COMPANY

W. E. Bishop, Ph. D.
Manager
Regulatory & Government Affairs
The Procter & Gamble Company
Telephone: 513/627-6368

Material Identity (SI0801.01)

Name: Amines, C10-16-alkyldimethyl, N-oxides, CASRN 70592-80-2

Weight %	31.9%
Peroxide Value	0.16 weight %
Free Amine	0.1 weight %
Color	17 (APHA)
pH	7.2

RESEARCH Argus LABORATORIES

Argus Research Laboratories, Inc.
905 Sheehy Drive, Building A
Horsham, Pennsylvania 19044
T: (215) 443-8710 F: (215) 443-8587

May 27, 1998

Daniel S. Marsman, D.V.M., Ph.D., DABT
The Procter and Gamble Company
Ivorydale Technical Center
Room 3S40
5299 Spring Grove Avenue
Cincinnati, Ohio 45217

RE: Protocol 916-025P - Oral (Gavage) Dosage-Range Developmental Toxicity Study of SI0801.01 in Rats

Dear Dr. Marsman:

Enclosed are unaudited draft summary tables from the end of the in-life phase of the dosage-range developmental toxicity study. The following information summarizes the results of this study. An audited summary report will be prepared and forwarded to you as scheduled in the protocol. This information is being provided in support of dosages selected for the full developmental toxicity study.

Methodology:

Forty presumed pregnant Crl:CD®BR VAF/Plus® (Sprague-Dawley) rats were randomly assigned to five dosage groups (Groups I through V), eight rats per group. Solutions of the test substance, SI0801.01, were administered orally via gavage once daily to these naturally-bred female rats on days 6 through 19 of presumed gestation[a] (DGs 6 to 19) at dosages of 0 (Vehicle), 32.5, 100, 325 and 650 mg/kg/day. The vehicle was sterile water for injection. The dosage volume was 5 mL/kg, adjusted daily on the basis of the individual body weights recorded immediately before administration of the test substance.

Checks for viability were made twice daily. Clinical observations were recorded daily before dosage and approximately 60 minutes after administration. These observations were also recorded on the day sacrificed. Body weights were recorded daily during the

---

a. Effective May 4, 1998 (DGs 11 and 13), the remaining three rats in the 650 mg/kg/day dosage group were not dosed due to excess toxicity, but remained on study.

dosage period and on the day sacrificed. Feed consumption values were recorded on DGs 0, 6, 9, 12, 15, 18 and the day sacrificed.

All surviving rats were sacrificed on DG 20 and examined for the number and distribution of corpora lutea, implantation sites and uterine contents. A gross necropsy of the thoracic, abdominal and pelvic viscera was performed. Fetuses were weighed and examined for gross external alterations and sex.

Results:

A. Mortality, Clinical and Necropsy Observations

A.1.a. Mortality

In the 650 mg/kg/day dosage group, four of the eight rats were found dead, two on gestation day 7 (DG 7), one on DG 8 and one on DG 9, and one was moribund sacrificed on DG 11. In the 325 mg/kg/day dosage group, one of the eight rats was found dead on DG 20. These deaths were considered related to the test substance because dosage-dependent clinical observations and body weight loss were noted before death. All other rats survived until scheduled sacrifice.

A.1.a.1. Deaths

650 mg/kg/day

Rat 6784 was found dead the morning of DG 8. This rat had received two administrations of the test substance. Clinical observations were normal but this rat lost 14 g between DGs 6 to 7. The uterus contained 19 normally developing conceptuses. All maternal tissues appeared normal at necropsy.

Rat 6786 was found dead approximately 2 hours postdosage on DG 8. This rat had received three administrations of the test substance. Clinical observations included were red perioral substance, excess salivation, urine-stained abdominal fur, ptosis and soft/liquid feces on the day of death. This rat lost 31 g from DGs 6 to 8. The uterus contained 19 normally developing conceptuses. The lungs and trachea contained a red frothy material, but perfusion of the lungs, trachea and esophagus revealed no perforations. All other maternal tissues appeared normal at necropsy.

Rat 6788 was found dead approximately 1 hour postdosage on DG 8. This rat had received three administrations of the test substance. Clinical observations included excess salivation on DGs 7 and 8, and urine-stained abdominal fur and loss of righting reflex on DG 8. This rat lost 30 g from DGs 6 to 8. The uterus contained 16 normally developing conceptuses. The cardiac mucosa of the stomach appeared red at necropsy; all other maternal tissues appeared normal.

Rat 6789 was found dead the morning of DG 9 after three administrations of the test substance. Clinical observations included ptosis and excess salivation on DGs 7 and 8, urine-stained abdominal fur and loss of righting reflex on DG 8. This rat lost 18 g from DGs 6 to 8. The uterus contained 16 normally developing implantations. All maternal tissues appeared normal at necropsy.

325 mg/kg/day

Rat 6776 was found dead on DG 20. This rat was given all 14 administrations of the test substance. Clinical observations included excess salivation on DGs 14 to 19, chromorhinorrhea on DGs 16 and 19, labored breathing on DGs 18 and 19, urine-stained abdominal fur on DG 19 and gasping on DG 19. This rat generally gained weight until DG 17, and lost 29 g from DGs 17 to 19. All maternal tissues appeared normal at necropsy for moderate degree of autolysis. This rat was not pregnant.

A.1.b. Moribund Sacrifice

650 mg/kg/day

Rat 6790 was euthanized on DG 11 after six administrations of the test substance. Clinical observations included urine-stained abdominal fur on DGs 9 to 11, localized alopecia on DGs 10 to 11, red perinasal substance on DG 11, excess salivation on DGs 10 to 11, gasping on DG 11 and soft or liquid feces on DG 11. This rat lost 18 g from DG 6 to 11. The uterus contained 19 normally developing implantations. Necropsy revealed numerous red areas on the nonglandular surface of the stomach; all other tissues appeared normal.

A.2. Clinical Observations

Clinical observations during gestation considered related to the test substance were excess salivation at the 100, 325 and 650 mg/kg/day dosage level (first observed on DGs 17, 10 and 7, respectively); urine-stained abdominal fur at the 325 and 650 mg/kg/day dosage level (first observed on DGs 10 and 8, respectively); perinasal substance at the 325 and 650 mg/kg/day dosage level (first observed on DGs 10 and 11, respectively); chromorhinorrhea at the 325 and 650 mg/kg/day dosage level (first observed on DGs 16 and 12, respectively); gasping at the 325 and 650 mg/kg/day dosage level (first observed on DGs 10 and 11, respectively); labored breathing at the 325 and 650 mg/kg/day dosage level (first observed on DGs 10 and 11, respectively); perioral substance at the 325 and 650 mg/kg/day dosage level (first observed on DGs 10 and 8, respectively); and ptosis and soft or liquid feces at the 650 mg/kg/day dosage level (first observed on DG 8). Agonal signs of gasping and loss of righting reflex occurred at the 325 and 650 mg/kg/day dosages.

All other clinical observations were considered unrelated to the test substance because: 1) the incidences were not dosage-dependent; and/or 2) they occurred in only one rat.

These observations included perivaginal substance, incisors missing/broken and localized alopecia on the back, neck, underside, limbs and/or head.

A.3. Necropsy Observations

All necropsy observations were considered unrelated to the test substance because: 1) the incidences were not dosage-dependent; and/or 2) they occurred in only one rat. Hydrometra occurred in one rat in each of the 100 and 650 mg/kg/day dosage groups; these rats were not pregnant. Necropsy observations in rats that died were discussed previously.

B. Maternal Body Weights and Body Weight Changes

Maternal body weight gains for the 325 and 650 mg/kg/day dosage groups were decreased, compared to the control group, or body weight losses occurred during the dosage period (DGs 6 to 20 for the 325 mg/kg/day dosage group; DGs 6 to 12 for the 650 mg/kg/day dosage group). Reflecting these effects of the test substance, weight gains for the entire dosage period (DGs 6 to 20) and the entire gestation period (DGs 0 to 20) were reduced in the 325 mg/kg/day dosage group, compared to the control group. The surviving rats in the 650 mg/kg/day continued to have reduced body weight gains during the postdosage period for this group (DGs 14 to 20)

Maternal body weights and body weight gains for the 32.5 and 100 mg/kg/day dosage groups were generally comparable to control values over each interval tabulated.

C. Maternal Feed Consumption Values

Absolute (g/day) and relative (g/kg/day) feed consumption values for the 325 and 650 mg/kg/day dosage groups were decreased, compared to the control group, during the dosage period (DGs 6 to 20 for the 325 mg/kg/day dosage group; DGs 6 to 12 for the 650 mg/kg/day dosage group). Reflecting these effects of the test substance, feed consumption values for the entire dosage period (DGs 6 to 20) and the entire gestation period (DGs 0 to 20) were reduced in the 325 mg/kg/day dosage group, compared to the control group. Feed consumption for the surviving rats in the 650 mg/kg/day dosage group continued to be reduced during this group's postdosage period (DGs 14 to 20).

Absolute and relative feed consumption values for the 32.5 and 100 mg/kg/day dosage groups were generally comparable to control values over each interval tabulated.

D. Caesarean-Sectioning and Litter Observations

Caesarean-sectioning observations were based on 8, 8, 6, 7 and 2 pregnant rats with live litters in the five respective dosage groups.

All conceptuses were resorbed in the two litters in the 650 mg/kg/day dosage group. These dams were only administered the test substance on DGs 6 to 11 or DGs 6 to 13.

Increased early resorptions with a concomitant reduction in litter size occurred at the 325 mg/kg/day dosage, relative to the control group. One dam in the 325 mg/kg/day dosage group had all resorbed conceptuses. Fetal body weights were reduced at the 325 mg/kg/day dosage. These observations were considered effects of the test substance because they were dosage-dependent and associated with the excessive maternal toxicity observed at these dosages (death, numerous adverse clinical findings and decreased body weight and feed consumption values).

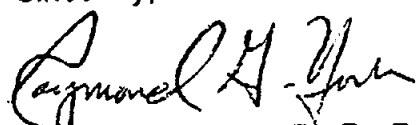
No Caesarean-sectioning or litter parameters were affected by dosages of the test substance as high as 100 mg/kg/day. The litter averages for corpora lutea, implantations, litter size, live fetuses, resorptions (early and late), dams with any resorptions, percent live male fetuses and fetal body weights were comparable among the 0 (Vehicle), 32.5 and 100 mg/kg/day dosage groups. There were no dead fetuses and no fetal gross external alterations observed at any of the dosages. One litter in the 32.5 mg/kg/day consisted of only three live male fetuses (average weight 5.63 g); inclusion of this litter tended to skew the values for implantations, litter sizes and fetal body weight in this group.

F. Recommendations

Based on the results of this study, dosages of 0 (Vehicle), 25, 100 and 200 mg/kg/day of the test substance, SI0801.01, are recommended for the full developmental toxicity study in rats. The 25 mg/kg/day dosage is expected to be a no-observable-adverse-effect-level (NOAEL) for both maternal and embryo-fetal toxicity and the 200 mg/kg/day dosage is expected to produce minimal maternal toxicity and little or no developmental toxicity.

If you have any questions, please do not hesitate to contact me.

Sincerely,



Raymond G. York, Ph.D., DABT
Associate Director of Research
and Study Director

ARGUS RESEARCH LABORATORIES, INC.

PROTOCOL 916025P : ORAL (GAVAGE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF SI0801.01 IN RATS (SPONSOR'S STUDY NUMBER: SIBTS97.042)

TABLE (PAGE 1): CLINICAL OBSERVATIONS - SUMMARY

TABLE RANGE : GESTATION PERIOD

DOSAGE GROUP	I	II	III	IV	V
MAXIMUM POSSIBLE INCIDENCE	168/ 8	168/ 8	168/ 8	168/ 8	112/ 8
APPEARS NORMAL	110/ 8	114/ 8	111/ 8	56/ 7	33/ 8
FOUND DEAD	0	0	0	1	4
MORIBUND SACRIFICE	0	0	0	0	1
SCHEDULED SACRIFICE	8	8	8	7	3
LOST RIGHTING REFLEX	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1
PTOSIS	0/ 0	0/ 0	0/ 0	0/ 0	6/ 4
PERINASAL SUBSTANCE	0/ 0	0/ 0	0/ 0	2/ 1	1/ 1
CHROMORHINORRHEA	0/ 0	0/ 0	0/ 0	2/ 1	3/ 1
PERIVAGINAL SUBSTANCE	0/ 0	0/ 0	0/ 0	5/ 2	0/ 0
ALOPECIA NO LONGER APPARENT	1/ 1	0/ 0	0/ 0	1/ 1	1/ 1
PERIORAL SUBSTANCE	0/ 0	0/ 0	0/ 0	1/ 1	3/ 2
EXCESS SALIVATION	0/ 0	0/ 0	2/ 2	49/ 8	18/ 7
INCISORS: MISSING/BROKEN	0/ 0	6/ 1	9/ 2	0/ 0	0/ 0
INCISORS: GROWN IN	0/ 0	0/ 0	1/ 1	0/ 0	0/ 0
GASPING	0/ 0	0/ 0	0/ 0	5/ 3	1/ 1
LABORED BREATHING	0/ 0	0/ 0	0/ 0	6/ 2	7/ 1

LOCALIZED ALOPECIA: BACK	10/ 1	0/ 0	0/ 0	0/ 0	2/ 1
LOCALIZED ALOPECIA: NECK	0/ 0	0/ 0	0/ 0	10/ 1	0/ 0
URINE-STAINED ABDOMINAL FUR	0/ 0	0/ 0	0/ 0	30/ 4	13/ 4
LOCALIZED ALOPECIA: UNDERSIDE	0/ 0	0/ 0	0/ 0	15/ 1	0/ 0
URINE-STAINED ABDOMINAL FUR	0/ 0	0/ 0	0/ 0	6/ 2	5/ 3
LOCALIZED ALOPECIA: LIMBS	0/ 0	0/ 0	0/ 0	0/ 0	4/ 1
LOCALIZED ALOPECIA: HEAD	0/ 0	0/ 0	0/ 0	3/ 1	0/ 0
SOFT OR LIQUID FECES	0/ 0	0/ 0	0/ 0	0/ 0	4/ 4

MAXIMUM POSSIBLE INCIDENCE = (DAYS x ANIMALS)/NUMBER OF ANIMALS EXAMINED PER GROUP

A R G U S R E S E A R C H L A B O R A T O R I E S , I N C .

PROTOCOL 916025P : ORAL (GAVAGE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF SI0801.0) IN RATS (SPONSOR'S STUDY NUMBER: SIRTS97.042)

TABLE (PAGE 1): MATERNAL BODY WEIGHTS - GESTATION - SUMMARY

DOSAGE GROUP DOSAGE		I 0 MG/KG/DAY	II 32.5 MG/KG/DAY	III 100 MG/KG/DAY	IV 325 MG/KG/DAY	V 650 MG/KG/DAY
RATS TESTED	N	8	8	8	8	8
PREGNANT	N(%)	8(100.0)	8(100.0)	6(75.0)	7(87.5)	7(87.5)
MATERNAL BODY WEIGHT (G)						
DAY 0	MEAN±S.D.	238.4 ± 16.3	237.9 ± 16.2	239.0 ± 14.5	240.1 ± 17.3	239.0 ± 15.4
DAY 6	MEAN±S.D.	274.5 ± 15.2	278.0 ± 18.9	272.7 ± 15.9	275.0 ± 21.7	273.4 ± 14.1
DAY 7	MEAN±S.D.	277.8 ± 15.5	278.5 ± 17.4	274.2 ± 16.0	274.0 ± 26.7	264.0 ± 16.8
DAY 8	MEAN±S.D.	285.2 ± 14.4	281.6 ± 18.7	275.8 ± 15.3	276.0 ± 25.8	256.8 ± 27.5 [6]
DAY 9	MEAN±S.D.	286.1 ± 19.5	288.1 ± 19.8	282.3 ± 16.8	279.3 ± 26.5	284.7 ± 7.8 [3]
DAY 10	MEAN±S.D.	295.6 ± 18.3	291.0 ± 19.7	287.0 ± 21.3	278.1 ± 36.2	282.0 ± 15.7 [3]
DAY 11	MEAN±S.D.	305.5 ± 16.5	297.8 ± 18.5	293.5 ± 22.4	276.3 ± 41.3	269.7 ± 39.1 [3]
DAY 12	MEAN±S.D.	310.8 ± 15.0	305.1 ± 20.7	302.5 ± 23.5	281.4 ± 37.6	277.0 ± 55.2 [2]
DAY 13	MEAN±S.D.	317.4 ± 16.5	309.6 ± 20.5	307.0 ± 20.4	284.8 ± 33.4	279.5 ± 31.8 [2]
DAY 14	MEAN±S.D.	320.6 ± 19.1	315.8 ± 22.0	311.3 ± 23.8	286.4 ± 43.2	268.5 ± 20.5 [2]
DAY 15	MEAN±S.D.	328.9 ± 16.6	326.6 ± 23.5	319.7 ± 22.6	297.7 ± 41.4	287.5 ± 31.8 [2]
DAY 16	MEAN±S.D.	341.4 ± 17.3	341.6 ± 26.4	334.0 ± 23.5	304.4 ± 45.9	294.0 ± 33.9 [2]
DAY 17	MEAN±S.D.	355.4 ± 19.8	355.8 ± 30.5	347.8 ± 22.2	317.6 ± 49.1	281.5 ± 58.7 [2]
DAY 18	MEAN±S.D.	374.6 ± 19.4	371.5 ± 33.3	366.5 ± 24.5	327.7 ± 52.2	272.0 ± 75.0 [2]
DAY 19	MEAN±S.D.	394.4 ± 23.7	389.4 ± 36.8	382.5 ± 27.0	339.0 ± 54.6	272.5 ± 87.0 [2]
DAY 20	MEAN±S.D.	414.6 ± 25.3	406.2 ± 41.4	400.3 ± 29.2	349.4 ± 57.7	273.0 ±101.8 [2]

This table restricted to pregnant animals.
DAY = DAY OF GESTATION
[ ] = NUMBER OF VALUES AVERAGED

A R G U S R E S E A R C H L A B O R A T O R I E S , I N C .

PROTOCOL 916025P : ORAL (GAVAGE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF SI0801.01 IN RATS (SPONSOR'S STUDY NUMBER: SIBTS97.042)

TABLE (PAGE 1): MATERNAL BODY WEIGHT CHANGES - GESTATION - SUMMARY

DOSAGE GROUP DOSAGE		I 0 MG/KG/DAY	II 32.5 MG/KG/DAY	III 100 MG/KG/DAY	IV 325 MG/KG/DAY	V 650 MG/KG/DAY
RATS TESTED	N	8	8	8	8	8
PREGNANT	N(%)	8(100.0)	8(100.0)	6(75.0)	7(87.5)	7(87.5)
MATERNAL BODY WEIGHT CHANGE (G)						
DAYS 0 - 6	MEAN±S.D.	+36.1 ± 13.9	+40.1 ± 12.3	+33.7 ± 7.9	+34.8 ± 7.6	+34.4 ± 11.1
DAYS 6 - 7	MEAN±S.D.	+3.2 ± 5.8	+0.5 ± 5.7	+1.5 ± 3.3	-1.0 ± 7.0	-9.4 ± 8.0
DAYS 7 - 8	MEAN±S.D.	+7.5 ± 2.7	+3.1 ± 6.6	+1.7 ± 5.3	+2.0 ± 2.4	-8.2 ± 12.5 [6]
DAYS 8 - 9	MEAN±S.D.	+0.9 ± 10.1	+6.5 ± 2.8	+6.5 ± 5.3	+3.3 ± 4.4	+6.3 ± 3.2 [3]
DAYS 6 - 9	MEAN±S.D.	+11.6 ± 12.6	+10.1 ± 2.9	+9.7 ± 3.1	+4.3 ± 9.4	-1.0 ± 5.2 [3]
DAYS 9 - 12	MEAN±S.D.	+24.6 ± 9.7	+17.0 ± 8.2	+20.2 ± 7.8	+2.1 ± 23.0	-6.5 ± 44.5 [2]
DAYS 6 - 12	MEAN±S.D.	+36.2 ± 8.6	+27.1 ± 9.8	+29.8 ± 9.0	+6.4 ± 25.3	-9.0 ± 50.9 [2]
DAYS 12 - 14	MEAN±S.D.	+9.9 ± 6.2	+10.6 ± 6.5	+8.8 ± 5.4	+5.0 ± 20.8	-8.5 ± 34.6 [2]
DAYS 14 - 18	MEAN±S.D.	+54.0 ± 7.0	+55.8 ± 15.8	+55.2 ± 4.1	+41.3 ± 16.9	+3.5 ± 54.4 [2]
DAYS 18 - 20	MEAN±S.D.	+40.0 ± 8.3	+34.8 ± 8.4	+33.8 ± 7.6	+21.7 ± 10.1	+1.0 ± 26.9 [2]
DAYS 14 - 20	MEAN±S.D.	+94.0 ± 12.9	+90.5 ± 22.4	+89.0 ± 7.7	+63.0 ± 25.2	+4.5 ± 81.3 [2]
DAYS 6 - 20	MEAN±S.D.	+140.1 ± 16.2	+120.2 ± 27.4	+127.7 ± 13.8	+74.4 ± 47.7	-13.0 ± 97.6 [2]
DAYS 0 - 20	MEAN±S.D.	+176.2 ± 19.6	+168.4 ± 33.0	+161.3 ± 16.8	+109.3 ± 46.5	+35.0 ± 93.3 [2]

This table restricted to pregnant animals.

DAYS = DAYS OF GESTATION

[ ] = NUMBER OF VALUES AVERAGED

PROTOCOL 916025P : ORAL (GAVAGE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF SI0801.01 IN RATS (SPONSOR'S STUDY NUMBER: SIBT397.042)

TABLE (PAGE 1): MATERNAL ABSOLUTE FEED CONSUMPTION VALUES (G/DAY) - GESTATION - SUMMARY

DOSAGE GROUP DOSAGE		I 0 MG/KG/DAY	II 32.5 MG/KG/DAY	III 100 MG/KG/DAY	IV 325 MG/KG/DAY	V 650 MG/KG/DAY
RATS TESTED	N	8	8	8	8	8
PREGNANT	N(%)	8(100.0)	8(100.0)	6(75.0)	7(87.5)	7(87.5)
MATERNAL FEED CONSUMPTION (G/DAY)						
DAYS 0 - 6	MEAN±S.D.	23.9 ± 2.3	24.2 ± 2.7	23.5 ± 1.7	24.8 ± 2.2	25.3 ± 2.1
DAYS 6 - 9	MEAN±S.D.	25.1 ± 3.6	24.8 ± 2.4	23.5 ± 2.3	21.4 ± 2.6	15.4 ± 7.2 [4]
DAYS 9 - 12	MEAN±S.D.	26.7 ± 1.5	24.9 ± 3.3	25.2 ± 3.9	18.0 ± 8.4	18.0 ± 14.1 [2]
DAYS 6 - 12	MEAN±S.D.	25.9 ± 2.2	24.8 ± 2.6	24.4 ± 3.0	19.7 ± 5.1	17.5 ± 11.6 [2]
DAYS 18 - 20	MEAN±S.D.	33.1 ± 1.7	29.9 ± 4.1	28.2 ± 3.0	24.3 ± 3.9	17.8 ± 21.6 [2]
DAYS 6 - 20	MEAN±S.D.	28.3 ± 1.4	27.3 ± 2.9	26.0 ± 2.4	22.6 ± 3.9	19.6 ± 9.9 [2]
DAYS 0 - 20	MEAN±S.D.	27.0 ± 1.5	26.4 ± 2.6	25.2 ± 2.1	23.2 ± 3.0	22.0 ± 7.1 [2]

This table restricted to pregnant animals.
DAYS = DAYS OF GESTATION
[ ] = NUMBER OF VALUES AVERAGED

A R G U S R E S E A R C H L A B O R A T O R I E S , I N C .

PROTOCOL 916025P : ORAL (GAVAGE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF SI0801.01 IN RATS (SPONSOR'S STUDY NUMBER: SIBTS97.042)

TABLE (PAGE 1): MATERNAL RELATIVE FEED CONSUMPTION VALUES (G/KG/DAY) - GESTATION - SUMMARY

DOSAGE GROUP		I	II	III	IV	V
DOSAGE		0 MG/KG/DAY	32.5 MG/KG/DAY	100 MG/KG/DAY	325 MG/KG/DAY	650 MG/KG/DAY
RATS TESTED	N	8	8	8	8	8
PREGNANT	N(%)	8(100.0)	8(100.0)	6(75.0)	7(87.5)	7(87.5)
MATERNAL FEED CONSUMPTION (G/KG/DAY)						
DAYS 0 - 6	MEAN±S.D.	93.2 ± 9.2	93.8 ± 6.4	92.0 ± 2.6	96.3 ± 6.8	98.8 ± 6.8
DAYS 6 - 9	MEAN±S.D.	89.4 ± 11.6	87.9 ± 6.8	85.0 ± 6.0	77.6 ± 9.0	63.1 ± 21.4 [3]
DAYS 9 - 12	MEAN±S.D.	89.2 ± 4.5	84.3 ± 9.3	86.2 ± 8.3	62.8 ± 24.4	62.6 ± 43.8 [2]
DAYS 6 - 12	MEAN±S.D.	89.1 ± 6.5	86.1 ± 7.3	85.6 ± 6.2	70.4 ± 13.8	61.6 ± 36.6 [2]
DAYS 18 - 20	MEAN±S.D.	83.9 ± 2.9	77.2 ± 10.0	73.7 ± 5.5	72.0 ± 7.6	55.2 ± 61.3 [2]
DAYS 6 - 20	MEAN±S.D.	87.0 ± 4.4	84.6 ± 6.8	81.8 ± 4.4	76.3 ± 12.2	68.6 ± 25.7 [2]
DAYS 0 - 20	MEAN±S.D.	84.3 ± 4.5	83.1 ± 5.0	80.7 ± 3.2	79.6 ± 9.8	79.0 ± 15.0 [2]

This table restricted to pregnant animals.
DAYS = DAYS OF GESTATION
[ ] = NUMBER OF VALUES AVERAGED

PROTOCOL 916025P : ORAL (GAVAGE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF SI0801.01 IN RATS (SPONSOR'S STUDY NUMBER: SIBTS97.042)

TABLE (PAGE 1): CAESAREAN-SECTIONING OBSERVATIONS - SUMMARY

DOSAGE GROUP		I	II	III	IV	V
DOSAGE		0 MG/KG/DAY	32.5 MG/KG/DAY	100 MG/KG/DAY	325 MG/KG/DAY	650 MG/KG/DAY
RATS TESTED	N	8	8	8	8	8
PREGNANT	N(%)	8(100.0)	8(100.0)	6(75.0)	7(87.5)	7(87.5)
DIED	N(%)	0	0	0	0	5(71.4)
ABORTED AND SACRIFICED	N(%)	0	0	0	0	0
DELIVERED	N(%)	0	0	0	0	0
ANIMALS PREGNANT AND CAESAREAN-SECTIONED ON DAY 20 OF GESTATION	N	8	8	6	7	2
CORPORA LUTEA	MEAN±S.D.	18.1 ± 2.1	19.4 ± 5.8	21.5 ± 6.0	17.0 ± 3.9	18.0 ± 0.0
IMPLANTATIONS	MEAN±S.D.	16.2 ± 0.7	16.2 ± 5.7	17.3 ± 1.4	15.7 ± 2.6	17.0 ± 0.0
LITTER SIZES	MEAN±S.D.	14.2 ± 3.1	15.6 ± 5.4	16.7 ± 1.6	10.8 ± 6.4	0.0 ± 0.0
LIVE FETUSES	N	114	125	100	76	0
	MEAN±S.D.	14.2 ± 3.1	15.6 ± 5.4	16.7 ± 1.6	10.8 ± 6.4	0.0 ± 0.0
DEAD FETUSES	N	0	0	0	0	0
	MEAN±S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
RESORPTIONS	MEAN±S.D.	2.0 ± 2.9	0.6 ± 0.5	0.7 ± 0.8	4.8 ± 5.7	17.0 ± 0.0
EARLY RESORPTIONS	N	15	5	4	33	34
	MEAN±S.D.	1.9 ± 2.5	0.6 ± 0.5	0.7 ± 0.8	4.7 ± 5.8	17.0 ± 0.0
LATE RESORPTIONS	N	1	0	0	1	0
	MEAN±S.D.	0.1 ± 0.4	0.0 ± 0.0	0.0 ± 0.0	0.1 ± 0.4	0.0 ± 0.0
DAMS WITH ANY RESORPTIONS	N(%)	7(87.5)	5(62.5)	3(50.0)	6(85.7)	2(100.0)
DAMS WITH ALL CONCEPTUSES DEAD OR RESORBED	N(%)	0	0	0	1(14.3)	2(100.0)
DAMS WITH VIABLE FETUSES	N(%)	8(100.0)	8(100.0)	6(100.0)	6(85.7)	0

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TABLE (PAGE 1): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - SUMMARY

DOSAGE GROUP		I	II	III	IV	V
DOSAGE		0 MG/KG/DAY	32.5 MG/KG/DAY	100 MG/KG/DAY	325 MG/KG/DAY	650 MG/KG/DAY
LITTERS WITH ONE OR MORE LIVE FETUSES	N	8	8	6	6	0
IMPLANTATIONS	MEAN±S.D.	16.2 ± 0.7	16.2 ± 5.7	17.3 ± 1.4	16.2 ± 2.6	-
LIVE FETUSES	N	114	125	100	76	0
	MEAN±S.D.	14.2 ± 3.1	15.6 ± 5.4	16.7 ± 1.6	12.7 ± 4.6	-
LIVE MALE FETUSES	N	59	61	61	35	0
% LIVE MALE FETUSES/LITTER	MEAN±S.D.	51.2 ± 10.5	54.2 ± 21.2	60.7 ± 12.7	49.4 ± 14.6	-
LIVE FETAL BODY WEIGHTS (GRAMS)/LITTER	MEAN±S.D.	3.55 ± 0.22	3.80 ± 0.76	3.50 ± 0.21	3.18 ± 0.37	-
MALE FETUSES	MEAN±S.D.	3.60 ± 0.25	3.86 ± 0.76	3.56 ± 0.22	3.26 ± 0.38	-
FEMALE FETUSES	MEAN±S.D.	3.50 ± 0.20	3.48 ± 0.18 [7]	3.35 ± 0.28	3.07 ± 0.40	-
% DEAD OR RESORBED CONCEPTUSES/LITTER	MEAN±S.D.	12.4 ± 18.0	3.5 ± 3.0	3.9 ± 4.8	20.5 ± 28.4	-

[ ] = NUMBER OF VALUES AVERAGED

NOTE: - Animals with all implants resorbing excluded from this table.